



REPLY TO
ATTENTION OF

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH VA 22041-3258



MCMR-RCQ (70-1n)

27 February 2002

HSRRB Policy Memorandum 02-01, Version 01

SUBJECT: Reporting to the HSRRB Unanticipated Problems Involving Risks to
Subjects or Others

1. REFERENCES.

- a. 21 Code of Federal Regulation (CFR) 56, *Institutional Review Boards*
- b. 21 CFR 312, *Investigational New Drug (IND) Application*
- c. 21 CFR 812, *Investigational Device Exemption*
- d. 32 CFR 219, *Federal Policy for the Protection of Human Subjects (Common Rule)*
- e. Department of Defense Directive (DoDD) 3216.2, *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research*, Coordinating Draft of 19 October 2001
- f. Army Regulation (AR) 40-7, *Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances* (Draft of Sep 2001 submitted to Department of the Army Judge Advocate General for final administrative review)
- g. AR 70-25, *Use of Volunteers as Subjects of Research*, 25 January 1990
- h. *International Conference on Harmonisation (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use, Good Clinical Practice: Consolidated Guideline (E6)*, 1997
- i. *Food and Drug Administration (FDA) Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators*, 1998
- j. *Institutional Review Board Reference Book*, PriceWaterhouseCoopers LLP, Washington, DC, 2001

2. HISTORY. This is the first version of HSRRB Policy Memorandum 02-01. This version is effective 4 March 2002. Details of the history can be found in Appendix A.

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3. PURPOSE. This policy establishes standardized requirements for reporting to The Surgeon General's Human Subjects Research Review Board (HSRRB) unanticipated problems involving risks to subjects or others. Requirements for reporting to the IRB of record should be included in the IRB's human subjects protection policies and procedures.

4. SCOPE. This policy applies to all investigators and medical monitors involved in intramural or extramural human subjects research conducted or managed by the U.S. Army Medical Research and Materiel Command (USAMRMC) and to any other human subjects research reviewed by the HSRRB. Any additional reporting requirements of pharmaceutical or medical device sponsors regarding unanticipated problems involving risks to subjects or others also will be followed.

5. DEFINITIONS.

a. Adverse Event (AE). "An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product." (ICH E6)

b. IRB of Record. The institutional review board, ethical review board, or human use review committee with primary responsibility for oversight of the research (FDA Information Sheets). The HSRRB generally serves as a second level review board, but there are exceptions for which the HSRRB serves as the IRB of record.

c. Investigator. "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." (ICH E6)

d. Medical monitor. "For research involving more than minimal risk (as defined in 32 CFR 219.102), to subjects, an independent medical monitor shall be appointed by name. Medical monitors shall be physicians, dentists, psychologists, nurses, or other health care providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate. Depending on the nature of the study, the medical monitor may be assigned to assess one or more of the following phases of a research project: subject recruitment, subject enrollment, data collection, or data storage and analysis. At the discretion of the IRB, the medical monitor may be assigned to discuss research progress with the principal

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investigator, interview subjects, consult on individual cases, or evaluate adverse event reports. Medical monitors shall promptly report discrepancies or problems to the IRB. They shall have the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the medical monitor's report." (DoDD 3216.2)

e. Unanticipated Problem Involving Risks to Subjects or Others. "An unanticipated problem involving risks to subjects or others is one that does not appear as a risk in the informed consent document and/or the protocol." (Institutional Review Board Reference Book). For the purpose of this policy, unanticipated problems also include any serious adverse drug experience, unexpected adverse drug experience, or unanticipated adverse device effect.

f. Serious Adverse Drug Experience. "Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of an existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse." (21 CFR 312.32)

g. Unexpected Adverse Drug Experience. "Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product." (21 CFR 312.32)

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h. Unanticipated Adverse Device Effect. "An unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." (21 CFR 812.3)

6. POLICY.

a. To enhance the protection of research subjects during the conduct of research and to facilitate a deliberate consideration of risks and benefits from the research during the IRB review, known risks of the research will be clearly identified in the research protocol and consent form. In addition to describing risks associated with the research, appropriate measures taken to minimize those risks will be identified in the protocol and consent form.

b. The Federal Policy (32 CFR 219) and FDA regulation (21 CFR 56) require IRBs to have written procedures for ensuring prompt reporting to the IRB, institutional officials, and the department or agency head of any unanticipated problems involving risks to subjects or others. Reports submitted to the HSRRB fulfill the requirement of notification of the department or agency.

c. Investigators will report to the IRB of record and the HSRRB any unanticipated problems involving risks to human subjects or others. Reports will be submitted immediately. This means within one day of discovery of the unanticipated problem. Investigators should contact the Acting Chair, HSRRB with any questions about interpretation of what to report to the HSRRB.

d. Reports to the HSRRB will be sent to the Acting Chair, HSRRB. The preferable mode of submission is facsimile to 301-619-7803 (DSN 343). Alternate modes of reporting include electronic mail to HSRRB@det.amedd.army.mil or telephone to 301-619-2165 (DSN 343).

(1) Data elements to include in reports are identified on the form that can be found in Appendix B. This form may be used for reporting the event, or an institutional specific form or study specific form may be used as long as all data elements are submitted.

(2) Investigators will submit follow-up reports until resolution of the unanticipated problem. Follow-up reports will be submitted to describe additional information that was not available at the time of the initial report, changes in the health status of the research subject, and ultimate outcomes associated with the unanticipated problem.

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(3) The investigator is responsible for informing the medical monitor of unanticipated problems involving risks to research subjects or others.

e. Medical monitors will provide an unbiased written report within ten calendar days of the initial report. At a minimum, the medical monitor will comment on the outcomes of the adverse event and the relationship of the event to participation in the study. The medical monitor will also indicate whether he/she concurs with the details provided in the report submitted by the investigator.

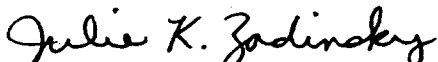
f. Medical monitor and follow-up reports may be reported via facsimile, e-mail, or mail to Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ (Acting Chair, HSRRB), 504 Scott Street, Fort Detrick, MD 21702-5012.

g. Appropriate supporting documents that should be submitted with the unanticipated problem report include, but are not limited to, laboratory reports, pathology reports, and discharge summaries.

h. All other adverse events from research will be reported to the IRB of record in accordance with more definitive requirements in the IRB's human subjects protection policies and procedures. Protocols will include procedures and appropriate forms for the recording of all adverse events. The continuing review report submitted to the IRB of record will contain a compilation of all adverse events and unanticipated problems involving human subjects and others from the reporting period. The compilation will also include a brief description of the respective outcomes associated with the adverse events and unanticipated problems. If the HSRRB is the IRB of record, the continuing review report will be submitted to the Acting Chair, HSRRB, in sufficient time to allow presentation to the HSRRB prior to the scheduled review date.

i. The HSRRB will evaluate reported information to determine if changes are warranted in the research protocol or protocol-related documents or in the information provided to research subjects. Any changes required by the IRB of record should be communicated immediately to the HSRRB. In the event of a discrepancy between the recommendations from the IRB of record and the HSRRB, the more restrictive recommendations will apply.

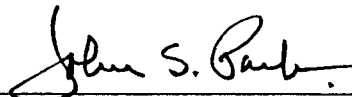
2 Encls


JULIE K. ZADINSKY
COL, AN
Acting Chair, Human Subjects
Research Review Board

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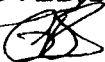
RECOMMEND APPROVAL/~~DISAPPROVAL~~



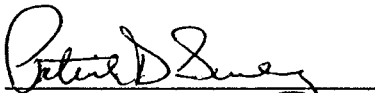
JOHN S. PARKER
Major General, MC
Chair, Human Subjects
Research Review Board

DATE:

1 March 2002


~~APPROVED/DISAPPROVED~~

FOR THE SURGEON GENERAL



PATRICK D. SCULLEY
Major General
Deputy Surgeon General

DATE: 4 Mar 02

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APPENDIX A
HSRRB Policy Memorandum History

Version Number: 01

Version Date: 27 February 2002

Effective Date:

Reasons for Revisions: This is the initial policy.

Detailed List of Changes: N/A

SUBJECT: HSRRB Policy Memorandum 02-01, Reporting to the HSRRB Unanticipated Problems Involving Risks to Subjects or Others

Report of Unanticipated Problem Involving Risks to Subjects or Others

Human Subjects Research Review Board (HSRRB)

MCMR-RCQ ♦ 504 Scott Street ♦ Fort Detrick, MD 21702-5012

301-619-2165/ DSN 343-2165/ Fax 301-619-7803

For any section in which additional space is needed, complete on plain bond paper.

Report Type (Circle One): Initial Follow-up Medical Monitor

HSRRB Log No: A-

Study Title:

Name of Principal Investigator:

Study Drug/Device, Including IND/IDE Number (if applicable):

Reporting Individual (Print name, title/position, and phone number.):

Total Study Enrollment to Date: _____ # Subjects/Participants _____ # Withdrawals
 _____ # Deaths

Subject Data: Subject ID _____ Age _____ Gender _____

Study Group/Arm _____ Enrollment Site _____

Unanticipated Problem Description (Include admission/discharge dates, event resolution if known, and subject status. Attach supporting documents, such as discharge summaries and lab reports. Remove personal identifiers on all supporting documents.):

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APPENDIX B

Report of Unanticipated Problem Involving Risks to Subjects or Others

Seriousness (check all that apply):	Relationship to drug/device/intervention	
Fatal	Not Related	Not Applicable
Life Threatening	Possibly	Probably
Disability	Definitely Related	
Hospitalization (initial or prolonged)	Unclassifiable	
Other (specify)		

Pertinent Medical History, Including Medication Use:

Actions Taken or Anticipated Actions in Response to this Unanticipated Problem (Explain any changes made to the consent form or protocol, whether the blind was broken, whether the study subject was dropped from the study, whether the event abated if the study article was discontinued, and any other significant actions taken or anticipated.):

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APPENDIX B

Report of Unanticipated Problem Involving Risks to Subjects or Others

Unanticipated Problem Reported to IRB of Record (Circle One): YES NO N/A

Date Reported to IRB of record:

Evaluation of the IRB of record:

Other Unanticipated Problems and Adverse Events Reported for this Study:

For Medical Monitor Reports Only - Assessment of Report from the PI (Comment on concurrence/non-concurrence with PI's report of diagnosis, treatment, and relationship of the unanticipated problem to the subject's participation in the study.):

Name and Signature of Individual Submitting the Report

Date